Anxiolytics, Adrenergic Agents, and Naltrexone

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ABSTRACT

Objective: To review extant data on the efficacy and safety of anxiolytic medications (benzodiazepines, buspirone, and other serotonin 1A agonists), adrenergic agents (β-blockers and α_2-adrenergic agonists clonidine and guanfacine), and the opiate antagonist naltrexone that have been used to treat various psychopathologies in children and adolescents. To identify critical gaps in our current knowledge about these agents and needs for further research. **Method:** All available controlled trials of these medications in children and adolescents published in English through 1997 were reviewed. In addition, selected uncontrolled studies are included. **Results:** The major finding, that there are virtually no controlled data that support the efficacy of most of these drugs for the treatment of psychiatric disorders in children and adolescents, is both surprising and unfortunate. For some drugs, e.g., buspirone and guanfacine, this is because no controlled studies have been carried out in children and/or adolescents. For other drugs, e.g., clonidine and naltrexone, most of the placebo-controlled studies have failed to demonstrate efficacy. **Conclusions:** The strongest recommendations for controlled studies of safety and efficacy in children and adolescents can be given for the following drugs: benzodiazepines for acute anxiety; buspirone (and newer serotonin 1A agonists as they become available) for anxiety and depression; β-blockers for aggressive dyscontrol; guanfacine for attention-deficit/hyperactivity disorder; and naltrexone for hyperactivity, inattention, and aggression in autistic disorder. *J. Am. Acad. Child Adolesc. Psychiatry,* 1999, 38(5):546–556. **Key Words:** psychopharmacology, pediatric, drugs.

This review examines safety and efficacy data for several groups of medications that are used to treat psychiatric disorders in children and adolescents. Classes of medications reviewed are the anxiolytics (benzodiazepines, buspirone, and other serotonin [5-HT] 1A agonists), adrenergic agents (the β-blockers and the α_2-adrenergic agonists clonidine and guanfacine), and the opiate antagonist naltrexone. Other classes of drugs that are used as anxiolytics, e.g., the tricyclic antidepressants and the selective serotonin reuptake inhibitors, are reviewed elsewhere in this Special Section (see Emslie et al., 1999; Geller et al., 1999).

All controlled trials of the selected medications in children and adolescents published in English through 1997 are included in this review. In addition, selected uncontrolled studies are included.

Each section follows a consistent format: background, efficacy, safety, and conclusions with recommendations for further research.

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BENZODIAZEPINES

BACKGROUND

Benzodiazepines have muscle relaxant, anticonvulsant, hypnotic, and antianxiety effects (Dantzer, 1985). Benzodiazepines have been studied widely in adults, but only a few controlled studies in children and adolescents have been reported and conclusions are limited by small sample sizes, short duration of medication trials, low dosages, and high placebo response rates. Benzodiazepines are in general absorbed and metabolized more rapidly in children than in adults (Siméon, 1993), but no specific

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pharmacokinetic data in children and adolescents are available for any of the benzodiazepines except diazepam (Clein and Riddle, 1995).

EFFICACY

Anxiety Disorders

Open-Label Studies. Of 18 children and adolescents with separation anxiety disorder treated with alprazolam (0.5–6 mg/day), 89% were rated improved by psychiatrists, 82% by parents, 65% by self-reports, and 64% by teachers (R. Klein, personal communication, 1991, cited by Kutcher et al., 1992). In another study, 4 adolescents with panic disorder improved on clonazepam 0.5 mg twice a day (Kutcher and MacKenzie, 1988). Somatic symptoms of anxiety improved more quickly than psychological symptoms of anxiety.

Placebo-Controlled Studies. In an 8-week double-blind study comparing alprazolam (mean daily dosage of 1.4 mg/day), imipramine (mean dosage of 135 mg/day), and placebo in children and adolescents with anxiety and/or depressive disorders, there was a trend in favor of the active medication groups (Bernstein et al., 1989). However, it was unclear whether the results were affected by baseline differences in symptom severity between the groups. In a double-blind, placebo-controlled study of alprazolam (mean dosage 1.6 mg/day, range 0.5–3.5 mg/day) for 4 weeks in 30 children and adolescents with overanxious disorder or avoidant disorder, 88% of the completers on alprazolam improved versus 62% in the placebo group, but this difference was not statistically significant (Siméon et al., 1992). A double-blind crossover study evaluated 4 weeks of clonazepam (0.5–2.0 mg/day) versus 4 weeks of placebo in 15 children with anxiety disorders, mainly separation anxiety disorder (Graae et al., 1994), without finding a significant difference between treatment arms. A double-blind, placebo-controlled study of clonazepam for adolescents with panic disorder demonstrated benefit with active medication (Kutcher and Reiter, personal communication, 1996). Those treated with clonazepam showed improvement on measures of generalized anxiety, frequency of panic attacks, and school and social disability.

Anxiety Associated With Medical Procedures

In 13 pediatric oncology patients, an open-label study of low-dose alprazolam (0.125–1.0 mg) showed the drug to be effective in decreasing anticipatory and acute situational anxiety associated with bone marrow aspirations and spinal taps (Pfefferbaum et al., 1987b). A double-blind, placebo-controlled study evaluated 0.2 mg/kg of oral midazolam, a high-potency, short-acting benzodiazepine, in preschool children undergoing laceration repair (Hennes et al., 1990). Midazolam is currently available only as a parenteral injection solution. Seventy percent in the midazolam group (21/30) improved versus 12% (3/25) in the control group ($p < .0001$). There were no respiratory or other adverse events.

SAFETY

As in adults, drowsiness and sedation are the most common side effects observed in children. These side effects are dose-related and generally resolve as tolerance develops (DuPont and Saylor, 1992). Other potential side effects include incoordination, diplopia, tremor, and decreased mental acuity (Biederman, 1991; Kutcher et al., 1992). Behavioral disinhibition in children is manifested by irritability, tantrums, and aggression (Graae et al., 1994), and in adolescents as irritability and behavioral outbursts (Reiter and Kutcher, 1991). In a report of 4 children with behavioral disinhibition on clonazepam, 3 of the children had underlying structural brain damage (Commander et al., 1991). These authors suggested that brain injury may be a risk factor for developing this adverse effect. Psychotic reactions or exacerbation of psychotic symptoms have also been reported. Pfefferbaum and colleagues (1987a) described 2 cases of exposure to low-dose benzodiazepines which were associated with psychotic symptoms, which resolved upon discontinuation of benzodiazepines.

Tolerance of and dependence on benzodiazepines occur in adults (Salzman, 1989). No data have been published regarding the risk of physiological and psychological dependence in children and adolescents. However, it is recommended that benzodiazepines be prescribed for youth on a short-term basis (i.e., weeks rather than months) because of the theoretical potential for dependence. Discontinuation of the benzodiazepines can be associated with recurrence of anxiety, rebound anxiety, and withdrawal symptoms such as anxiety, malaise, irritability, headache, sweating, gastrointestinal symptoms, insomnia, and muscle tension (Coffey, 1993; Salzman, 1990). Gradual tapering of the drug reduces the risk of developing these symptoms (Coffey, 1993; DuPont and Saylor, 1992; Kutcher et al., 1992). Abrupt discontinuation of benzodiazepines can result

in seizures, especially in patients with a history of seizures. For clonazepam, a discontinuation rate of less than 0.04 mg/kg per week was found to be safe in a prospective study (Sugai, 1993). Benzodiazepines are relatively safe in overdose (Kutcher et al., 1992), yet these drugs have additive effects with other sedative and hypnotic drugs, including alcohol (Green, 1995). The rate of absorption of the benzodiazepines and the magnitude of their CNS depression effects are also increased by alcohol (Rall, 1990).

Unprescribed use of benzodiazepines occurs in adolescence. In a longitudinal study of 1,230 teenagers in Sweden, 10% had taken anxiolytic and/or hypnotic medications in the previous year (Pedersen and Lavik, 1991). The majority gave sleep disturbance, depression, or minor life stressors as explanations for taking the drugs. Two thirds of the teenagers received the benzodiazepines from their parents, primarily their mothers. On the other hand, 13% of the males and 20% of the females reported intoxication as the purpose for taking these drugs. In this group, the benzodiazepines were obtained from peers and illegal sources. There was a strong association between use by parents and unprescribed use by the adolescents, suggesting that the teenagers were modeling their parents' use.

RECOMMENDATIONS FOR FURTHER RESEARCH

Future work should focus on controlled studies with adequate sample size, dosage, and duration of treatment to address efficacy of the benzodiazepines for anxiety disorders in children and adolescents. For those benzodiazepines that demonstrate clinical efficacy, pharmacokinetic studies need to be conducted. In addition, studies that evaluate medication in combination with psychosocial treatment are desirable, as they more closely mimic treatment in the real world. It is also important to study tolerance and dependence so that clinicians will be guided regarding which youth are candidates for benzodiazepines and how long treatment should last. The long-term safety of this class of medication needs to be addressed.

BUSPIRONE AND OTHER 5-HT_{1A} AGONISTS

BACKGROUND

The 5-HT_{1A} receptor agonists enhance the tonic activation of postsynaptic 5-HT receptors by acting to desensitize the 5-HT_{1A} receptor located on the somatodendritic portion of the presynaptic neuron (Blier et al., 1990). This receptor is part of a negative feedback loop that limits release of 5-HT from the presynaptic neuron as synaptic 5-HT concentrations rise. In studies of adults, buspirone and other azaperone partial agonists at the 5-HT_{1A} receptor have been shown to have both anxiolytic and antidepressant properties. Controlled trials have shown that buspirone is effective for major depression (Rickels et al., 1991; Robinson et al.,1989) and generalized anxiety disorder (Ansseau et al., 1990; Enkelmann, 1991). Unlike gepirone (Pecknold et al., 1993), buspirone does not appear to be effective for panic disorder (Sheehan et al., 1993) or for obsessive-compulsive disorder as a primary agent (Pato et al., 1991) or as an augmentor (McDougle et al., 1993). Buspirone is the only 5-HT_{1A} agonist currently marketed in the United States (for generalized anxiety disorder in adults). Despite lack of controlled studies, buspirone is used in children and adolescents for indications as diverse as oppositional behavior, anxiety, and depression, in part because it is remarkably free of side effects (Kutcher et al., 1995). Other compounds active at pre- and postsynaptic 5-HT_1 receptors also are under development (Dubovsky, 1993; Mosconi et al., 1993). For example, flesinoxan (Rodgers et al., 1994), gepirone (McGrath et al., 1994), ipsapirone (Cutler et al., 1994), and tandospirone (Evans et al., 1994) have shown promise in adults.

EFFICACY

No pharmacokinetic, dose-finding, or controlled safety and efficacy studies of buspirone or any other 5-HT_{1A} agonist in mentally ill children or adolescents have been reported (Hughes and Preskorn, 1994; Kutcher et al., 1995). On the basis of open data, clinical experience, and age-downward extension of studies in adults, buspirone has been used for children with generalized anxiety (Coffey, 1990; Kutcher et al., 1992, 1995; Maletic et al., 1994; Popper, 1993). Moreover, it has been used in the following contexts: anxiety mixed with mild depression; affect-driven aggression in association with oppositional symptoms; pervasive developmental disorders, where affect dysregulation, aggression, and cognitive rigidity are problematic; and occasionally, attention-deficit/hyperactivity disorder (ADHD) refractory to more conventional treatments. However, until controlled studies are available, the use of buspirone for these indications must be considered preliminary.

In an open trial, Siméon (1993) treated 15 patients (aged 6–14 years) with anxiety disorders with buspirone for 4 weeks (18.6 mg mean maximum daily dose) and reported significant improvement in anxiety, behavior, and hyperactivity. Adverse events were infrequent and mild. Case reports of children and adolescents also suggest benefit in overanxious disorder (Kranzler, 1988), depression and obsessive-compulsive disorder (Alessi and Bos, 1991), and social phobia (Zwier and Rao, 1994). An interesting literature also has grown up around the use of buspirone in aggressive children (Gross, 1995; Mandoki, 1994; Stanislav et al., 1994), where speculation has it that benefit may accrue from dopamine antagonist properties seen at high doses as well as from modulation of serotonergic activity, and in autistic children (Realmuto et al., 1989), where attention, impulse control, and hyperactivity have reportedly decreased in some patients. A recently published open-label study in 25 prepubertal children with anxiety and aggression tested doses of up to 50 mg/day for up to 9 weeks: 6 children showed increased aggression or mania, and of the 19 who completed the study only 3 had sufficient benefit to continue buspirone after the study (Pfeffer et al., 1997). Buspirone is usually started at 5 mg 3 times per day and gradually increased to 30, 60, and 90 mg/day in 3 divided doses every 2 weeks. The need for thrice-daily dosing limits feasibility and compliance. Time will tell whether compounds such as gepirone, with higher potency at the 5-HT_{1A} receptor than buspirone; transdermal (patch) delivery of buspirone, which allows much higher serum levels without excessive side effects and which one investigative group (Conners and March, personal communication, 1998) is studying for the treatment of ADHD; or longer-lived 5-HT_{1A} agonists may show greater benefit than the tablet form of buspirone in this regard.

SAFETY

Side effects across trials of patients with different disorders using different 5-HT_{1A} agonists have been uniformly mild: light-headedness, stomach upset, dizziness, sedation, asthenia, or headaches. Furthermore, the 5-HT_{1A} agonists cause no withdrawal symptoms even after prolonged administration (Rakel, 1990) and have no addictive potential (Murphy et al., 1989).

RECOMMENDATIONS FOR FURTHER RESEARCH

There is a need for rigorous, controlled studies of buspirone in children and adolescents with various anxiety disorders. In addition, the newer 5-HT_{1A} agonists, such as flesinoxan and gepirone, should be assessed for safety and efficacy in children with anxiety disorders. All of these agents are potentially attractive for use in children because of their favorable side effect profile.

β-BLOCKERS

BACKGROUND

The β-adrenergic blocking agents ("β-blockers") have been used for children and adolescents with anxiety disorders or aggressive dyscontrol, although systematic studies have not been done. The largest body of work actually exists for their use in children for treatment of nonpsychiatric disorders, such as migraine headache and neurally mediated syncope. For example, 36 children and adolescents with neurally mediated hypotension were treated with β-blockers, and the investigators concluded that they were safe and efficacious (Scott et al., 1995). Their role in prophylaxis of migraine headaches has been reported since the early 1980s (Forsythe et al., 1984).

There are essentially no pharmacokinetic data in children. β-Blockers differ on type (specificity) of β-receptor blockade, lipophilicity, elimination, and half-life. Propranolol and nadolol are nonselective β-blockers (at both β_1 and β_2 receptors), whereas atenolol and metoprolol are selective for β_1 receptors. These drugs differ on exerting central and peripheral effects, although it is not clear which may play a more important role in moderating anxiety symptoms. Propranolol and metoprolol have both central and peripheral effects, whereas nadolol and atenolol have very little central action. Propranolol and metoprolol undergo hepatic metabolism, whereas atenolol and nadolol are cleared by renal elimination. Propranolol is highly protein-bound, which has clinical import in terms of drug interactions. Drug–drug interactions have been reported in which β-blockers may increase the levels and effects of certain drugs, as well as decrease those of others, generally through competitive inhibition mechanisms. Gillette and Tannery (1994) reported on 2 children with nearly toxic plasma levels of imipramine when taking concomitant propranolol.

EFFICACY

Anxiety Disorders

Studies in adults have not shown significant effects of β-blockers over placebo in the treatment of social phobia,

panic disorder, performance anxiety, or posttraumatic stress disorder (PTSD) (Liebowitz et al., 1992; Turner et al., 1994), yet these agents are commonly prescribed for such disorders. Data in children are even more limited.

Open-Label Studies. Famularo and colleagues (1988) reported some improvement in 11 children with PTSD openly treated with propranolol up to 2.5 mg/kg per day using an on-off-on design. Joorabchi (1977) reported that propranolol (up to 30 mg/day) helped 13 of 14 adolescents with hyperventilation syndrome and suggested that this drug might be effective in treating panic disorder.

Placebo-Controlled Studies. No systematic studies of a β-blocker have been completed for any pediatric anxiety disorder.

Aggressive Dyscontrol

Open-Label Studies. Williams and colleagues (1982) reported that open treatment of propranolol in 30 patients (age ranged from 7 to 35 years) with organic brain dysfunction resulted in moderate to marked improvement of the aggression using high dosages (50–1,600 mg/day). Subsequent open trials have reported symptom improvement. Recently, a case report of a 14-year-old, multiply handicapped adolescent with severe self-injury reported a positive response to 300 mg of propranolol per day over a 12-month period (Lang and Remington, 1994). The authors hypothesized that individuals with mental retardation whose symptoms are characterized by overactivity, overarousal, poor frustration tolerance, and self-injurious behavior may be the target population, but more studies are needed.

Placebo-Controlled Studies. No placebo-controlled studies have been reported.

SAFETY

Side effects reported in children are generally similar to those in adults: sedation, mild hypotension, lowered heart rate, bronchoconstriction, hypoglycemia (in diabetic patients), dizziness, Raynaud phenomenon, and sleep disruption (Coffey, 1990). Major concerns in children are potential bradycardia, hypotension, and bronchoconstriction in asthmatic patients. Rebound hypertension is reported in adults upon abrupt withdrawal, so this risk can be avoided by a gradual discontinuation.

One possible effect that has received little attention is that of β-blockers on growth hormone (GH) regulation. Catecholamines inhibit GH secretion through β-adrenergic receptors. β-Blockers do not appear to stimulate GH when given alone, but a controlled study found that long-term administration of atenolol potentiated the growth-promoting effects of GH-releasing hormone therapy in growth-deficient children (Cassorla et al., 1995). β-Blockers can also suppress melatonin (Riddle et al., 1988). This effect has provided the rationale to treat winter depression with propranolol or atenolol (Schlager, 1994). The long-term effects of these neuroendocrine manipulations in children are unknown, and additional studies are needed.

RECOMMENDATIONS FOR FURTHER RESEARCH

This class of drugs needs further investigation regarding safety, efficacy, and pharmacokinetics. Controlled studies in patients with brain damage and aggression are particularly needed.

α-ADRENERGIC AGONISTS: CLONIDINE AND GUANFACINE

BACKGROUND

Since the 1960s, clonidine has been used to treat hypertension in adults (see Wilber, 1980). In the late 1970s, the psychiatric use of clonidine was initiated by Cohen and colleagues (1979) for the treatment of children with Tourette's and other tic disorders. Later this use was extended by Leckman and Cohen (1983) and Hunt and colleagues (1985) as an alternative to stimulant medications for the treatment of children with ADHD, alone or comorbid with Tourette's disorder. By the early 1990s, approximately 200,000 prescriptions per year were written in the United States (Swanson et al., 1995) for clonidine at doses of 0.05 to 0.10 mg administered multiple times during the day to treat children with ADHD (Hunt et al., 1990) and sometimes at night to treat spontaneous or stimulant-related sleep problems (Rubinstein et al., 1994; Wilens et al., 1994). At these doses, clonidine is considered to have agonist effects on presynaptic α_2-adrenergic receptors, which result in a net negative effect on noradrenergic activity by reducing its release (Svensson et al., 1975). At peak times, 2 to 6 hours after administration, this produces decreased sympathetic and increased para-

sympathetic tone and results in decreased activity, wakefulness, blood pressure, heart rate, and saliva flow.

EFFICACY

Attention-Deficit/Hyperactivity Disorder

Uncontrolled Studies. Uncontrolled studies of the effects of clonidine in children with ADHD have been reported. Hunt (1987) treated 8 children with ADHD with oral clonidine up to 5 μg/kg per day for 2 months, followed by a switch to an equivalent dose of transdermal clonidine, and concluded that the effects of clonidine were significant and about the same magnitude as the effects of methylphenidate (by comparison to a prior investigation of these same cases). Steingard et al. (1993) conducted an open clinical trial of oral clonidine (average dose of 0.19 mg/day) with 30 children with ADHD, half of whom had failed to respond to previous trials of stimulants or antidepressants, and reported clinical benefits in 16 (53%) of these cases. Interpretation of these studies is complicated by the different inclusion/exclusion criteria used in these studies.

Controlled Studies. In an 8-week, double-blind, placebo-substitution study of clonidine 4 to 5 μg/kg per day (about 0.05 mg q.i.d.) in 11 children with ADHD, significant improvement with effect sizes greater than 1.0 was reported in 7 children, based on parent and teacher ratings of hyperactivity and conduct problems (Hunt et al., 1985). Gunning (1992) used a double-blind, parallel-groups design with 3 groups of 24 children with ADHD, treated for 8 weeks with clonidine (0.03–0.05 mg/kg per day), methylphenidate (0.4–0.6 mg/kg per day), or placebo. Based on overall clinical improvement judged by a psychiatrist, the same percentage of subjects (50%, significantly greater than 13% on placebo) were judged to have improved on clonidine and methylphenidate, and significantly greater than placebo decreases in parent and teacher ratings were reported for clonidine (about 14%) and methylphenidate (about 20%). The interpretation of these studies is complicated by the selection criteria of the ADHD subjects, which limits generalizability. Also, the Gunning (1992) study was conducted in The Netherlands, which has a different tradition for the recognition of ADHD and use of stimulants, and a lower than expected response rate (50%) to methylphenidate was observed in this sample of ADHD cases. Moreover, as discussed further, in 3 of 5 controlled studies of the efficacy of clonidine for the treatment of Tourette's disorder, the effects of clonidine on behavior (symptoms of ADHD) were not significant.

Combination of Clonidine and Methylphenidate. Clonidine is often used in combination with methylphenidate (and other stimulant medications) to treat children with ADHD. Hunt (1987) and Hunt et al. (1990) suggested that the combination may lead to beneficial effects on activity, aggression, and oppositionality at lower doses of methylphenidate than usually used, but no experimental data in support of this hypothesis have been presented. Comings et al. (1990) made similar claims based on clinical experience with 41 children with ADHD (and a large number of additional cases with Tourette's disorder and conduct disorder), especially for the use of clonidine administered transdermally. There are no controlled studies to support the combined use. Interactions of the opposing mechanisms of action of these 2 medications may result in rare but serious side effects (Cantwell et al., 1997; and see below).

Tic Disorders and Tourette's Disorder

Uncontrolled Studies. Uncontrolled studies of the efficacy of clonidine for tics have produced conflicting results. In a briefly described, "open study" of transdermal clonidine in 210 patients with Tourette's disorder, "some improvement" was reported in 61% (Comings et al., 1990), but Steingard et al. (1994) reviewed clinical charts of 7 patients with comorbid tic disorders and ADHD who were treated with clonidine 0.1 to 0.3 mg/day and found a significant reduction in ADHD symptoms but not tics.

Controlled Studies. Several controlled studies have been conducted to evaluate the hypothesis (see Cohen et al., 1979) that clonidine is an effective treatment for Tourette's disorder, either alone or with comorbid ADHD. Two early studies did not confirm this hypothesis (Borison et al., 1982; Goetz et al., 1987), but Leckman et al. (1991) partially confirmed the hypothesis about tics in a parallel-groups, double-blind study of children with Tourette's disorder (half of whom had comorbid ADHD) treated with up to clonidine 0.25 mg/day (n = 24) or placebo (n = 23). Clinician ratings suggested a significant decrease in severity of tics but not in severity of hyperactivity/impulsivity, but parent ratings suggested the opposite pattern (a significant decrease in severity of symptoms of hyperactivity/impulsivity but not tics). In Gunning's (1992) double-blind, parallel-

groups study, groups of children with ADHD plus Tourette's disorder were treated for 8 weeks with clonidine 0.03 to 0.05 mg/kg per day (n = 16) or placebo (n = 16), but the hypothesis about tics was not confirmed: fewer subjects improved in the clonidine-treated group (25%) than in the placebo-treated group (31%). Singer et al. (1995) conducted a double-blind, crossover study of children with Tourette's disorder and ADHD (n = 34) treated with clonidine (0.05 mg q.i.d.), desipramine (100 mg/day), and placebo. Treatment with clonidine did not result in a significant decrease in parent ratings of tics or hyperactivity relative to ratings on placebo, but treatment with desipramine did produce a significant reduction in ratings of both tics and hyperactivity. Thus, in 4 of 5 placebo-controlled studies of treatment of Tourette's disorder, clonidine was no more effective than placebo in reducing the severity of tic symptoms. Overall, these controlled studies do not support the hypothesis that clonidine is an effective treatment for tics.

Aggression

Uncontrolled Studies. Improvement has been reported at doses up to 0.4 mg/day both in outpatients (by Dawson et al., 1989, in a case report of a child with explosive disorder; by Comings et al., 1990, who treated 41 children with conduct disorder; and by Kemph et al., 1993, who treated 17 children in crisis due to serious aggression) and in inpatients, often in combination with other psychotropic medications (by Schvehla et al., 1994, who treated 18 children with uncontrolled anger and aggression who had failed to respond to trials of stimulant medications, and by Chandran, 1994, who treated 60 children with uncontrolled anger and physical aggression). These results may be due (at least in part) to nonspecific sedative effects of clonidine or Hawthorne effects on the subjective measures of response, which cannot be discounted by the uncontrolled designs.

Sleep Disorders

Uncontrolled Studies. Rubinstein et al. (1994) reported that 0.05 to 0.1 mg of clonidine at night decreased sleep latency in 15 children who had sleep difficulties during treatment with methylphenidate for ADHD. Wilens et al. (1994) described the effects of 0.05 to 0.4 mg of clonidine administered at night to treat sleep problems in more than 100 children with ADHD (with spontaneous or stimulant-induced sleep problems) and reported sedation within 30 minutes which persisted until morning. Prince et al. (1996) described similar effects in a systematic chart review of 62 cases in which clonidine was used to treat sleep disturbances associated with ADHD.

Autism and Fragile X Syndrome

Uncontrolled Studies. Uncontrolled studies have suggested beneficial effects: Fankhauser et al. (1992) reported on the use of transdermal clonidine to treat 9 children with autism and reported decreases in "hyperarousal" noted by parents and clinicians. Hagerman et al. (1998) reported on the use of clonidine (alone or in combination with methylphenidate) to treat 35 children with fragile X syndrome and reported a perceived benefit (documented by parent interview) due to decreased hyperactivity, irritability, tantrums, and bedtime problems.

Controlled Studies. Jaselskis et al. (1992) performed a double-blind study of clonidine, 0.15 to 0.20 mg/day, to treat 8 children with autism and reported nonsignificant overall effects compared with placebo. Some ratings of aberrant (by teacher) and oppositional (by parent) behavior were decreased, but owing to side effects (hypotension and drowsiness), only 2 of the 8 patients could tolerate long-term treatment with clonidine.

SAFETY

Cardiac side effects (dysrhythmia, bradycardia, first-degree heart block, nonconducted P waves, sinus bradycardia, supraventricular premature complexes, nonspecific intraventricular conduction delay, T wave abnormality, and possible anterior ischemia) associated with the use of clonidine to treat psychiatric disorders in children have been reported (Chandran, 1994; Dawson et al., 1989), but in both cases other medications were used concurrently with clonidine, which complicates the interpretation of these adverse events. Other cardiac side effects have been reported in the Food and Drug Administration's MedWatch system. Swanson et al. (1995) summarized 23 MedWatch reports of adverse events in children receiving clonidine, of which 4 were reports of sudden death due to cardiac failure in children being treated with clonidine in combination with methylphenidate (with a calculated relative risk of sudden death of 25:1 for the combination compared with either clonidine or methylphenidate alone). These rare cases were also complicated by other factors including treatment with additional medications and preexisting cardiac abnormalities, which suggested to some an explanation of the sudden deaths (Fenichel, 1995;

Popper, 1995). Swanson et al. (1995) speculated that cardiovascular side effects might be triggered by a specific pharmacodynamic interaction between the 2 medications that would occur when the peak of clonidine effect with its potentiation of sedation-hypotension-bradycardia coincides with waning of the methylphenidate effects, or the peak effects of methylphenidate (i.e., activation-hypertension-tachycardia) occur when the effects of clonidine are decreasing. Cantwell et al. (1997) performed interviews of cases suspected of having adverse responses to this combination and suggested that dose-related threshold effects of clonidine may be responsible for the former pattern and that noradrenergic overdrive following abrupt clonidine withdrawal may be responsible for the latter pattern.

GUANFACINE

Uncontrolled Studies of ADHD. Guanfacine, a longer-acting and more selective α_2-adrenergic agonist than clonidine, has been hypothesized to have a selective effect on attention (see Arnsten et al., 1996). There are no controlled trials of guanfacine, but 2 uncontrolled studies have been reported. Hunt et al. (1995) conducted an open clinical trial of 13 children with ADHD treated for 4 weeks with titrated doses (average = 3.2 mg/day) and reported a perceived reduction based on parent ratings of hyperactivity, inattention, and immaturity but not mood problems or aggression. Chappell et al. (1995) conducted an open clinical trial of 10 children with Tourette's disorder and ADHD treated with 1.5 mg/day (for 4–20 weeks) and reported a confusing pattern of pre–post differences in subjective ratings: clinician ratings suggested a reduction in phonic tics but not motor tics, self-ratings suggested a reduction of motor tics but not phonic tics, and parent ratings suggested no significant effect on overall behavior. Improved pre–post performance on a continuous performance task was reported (reduction in commission errors from 3.1 to 0.2 and omission errors from 6.1 to 0.4), but this uncontrolled trial cannot discount a practice effect or a floor effect as alternative explanations rather than an effect of guanfacine.

RECOMMENDATIONS FOR FURTHER RESEARCH

The lack of support from controlled trials for the efficacy of clonidine for the treatment of tics and/or ADHD suggests that additional controlled trials may not be needed for these indications. An ongoing, multisite, parallel-groups comparison of methylphenidate, clonidine, methylphenidate plus clonidine, and placebo in children and adolescents with ADHD plus tics should provide definitive data regarding safety and efficacy (R. Kurlan, personal communication, 1998). The encouraging results of uncontrolled studies of clonidine for aggression and sleep problems in children identifies a critical need for controlled studies of this established and increasing clinical practice.

Guanfacine has some potential advantages over clonidine: longer half-life and selectivity for the α_2-adrenergic receptors, which are located primarily in the prefrontal cortex and may affect attention. Controlled trials of the safety and efficacy of guanfacine in the treatment of ADHD symptoms, aggression, and tics would be valuable now, to avoid the existing situation of uncertainty about the clinical use of clonidine.

NALTREXONE

BACKGROUND

Excessive endogenous opioid activity is hypothesized to induce "emotional numbing" in PTSD (Clover, 1993). Consistent with this hypothesis, a preliminary uncontrolled trial of the opiate antagonist nalmefene led to reduced numbing in war veterans with PTSD (Clover, 1993). There are no published studies of opiate antagonists to treat anxiety disorders in children and adolescents.

Naltrexone is an opiate antagonist which has been a focus of research investigation in autistic disorder since Panksepp (1979) proposed that increased opiate activity may underlie social and behavioral abnormalities in autism. This hypothesis is strengthened by the finding of an elevated cerebrospinal fluid (CSF) opiate fraction in subjects with autism (Gillberg et al., 1983, 1985) and an elevation of C-terminally directed β-endorphin immunoreactivity in subjects with autism relative to control subjects (Leboyer et al., 1994).

EFFICACY

Uncontrolled Studies. Initial reports of naltrexone treatment in autistic disorder led to excitement that the core social deficits of autistic disorder might be responsive (Campbell et al., 1988; Herman et al., 1986).

Controlled Studies. Controlled trials have shown no effects on core symptoms of autistic disorder. A reduc-

tion in hyperactivity has been the most consistent effect of naltrexone in autistic patients. In the most extensive publication of a controlled trial to date, 41 hospitalized children were treated with naltrexone, 1 mg/kg/day for 3 weeks. Random, blinded assignment to either placebo or drug was performed. Children's Psychiatric Rating Scale ratings of hyperactivity, as well as automated laboratory measures of activity, were reduced in the group treated with naltrexone (Campbell et al., 1993). This finding is supported by 3 other controlled trials (Herman et al., 1993; Kolmen et al., 1997; Willemsen-Swinkels et al., 1995). No significant effect on self-injurious behavior was detected (Campbell et al., 1993; Willemsen-Swinkels et al., 1995), but these studies had low power because relatively few subjects had at least moderately severe self-injurious behavior.

SAFETY

Naltrexone-associated liver toxicity has occurred in adults with a history of drug and alcohol abuse. No laboratory abnormalities were found in 21 children after 3 weeks of treatment with 1.0 mg/kg per day (Campbell et al., 1993). Side effects were mild: drowsiness (in 13%), anorexia (9%), and vomiting (13%). Similar results have been found in other studies (Kolmen et al., 1997). There are, however, no long-term studies in children.

A single trial of the use of naltrexone in Rett's disorder revealed more rapid decline in motor function and more rapid progression of the disorder in 10 patients receiving naltrexone compared with controls (Percy et al., 1994). Thus, naltrexone is contraindicated in Rett's disorder. There are no data on the effects of combining naltrexone with other agents.

RECOMMENDATIONS FOR FURTHER RESEARCH

There is no evidence in support of the efficacy of naltrexone on the core social and cognitive deficits of autistic disorder or in the reduction of rituals and routines. But based on the 4 controlled studies that reported a reduction of hyperactivity in children with autistic disorder, controlled long-term safety and efficacy studies of the effect of naltrexone on hyperactivity, impulsivity, and inattention in autism are warranted. Both subjects with autistic disorder accompanied by self-injurious behavior and nonautistic mentally retarded subjects with self-injurious behavior should be studied. Drug effects should be tested in the context of appropriate educational, behavioral, and psychotherapeutic interventions. Consideration should be given to study naltrexone in normally developed children with ADHD, particularly in patients with tics who worsened while they were taking stimulants. With the recent cloning of the opiate receptors, molecular-genetic and molecular-neurobiological studies may lead to the development of improved opiate antagonist agents.

CONCLUSIONS

Among this heterogenous group of pharmacological agents, there a several compounds that are commonly prescribed to children for the treatment of specific psychopathologies. Their use contrasts with the dearth of experimental data in support of their efficacy and safety and calls for systematic investigation. In this review we have outlined specific recommendations for further research on the most promising compounds.

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